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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER
HELMS, LARRY RONALD

ART UNIT	PAPER NUMBER
1642	10

DATE MAILED: 11/12/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/807,007	ZAPHIROPOULOS ET AL.	
	Examiner	Art Unit	
	Larry R. Helms	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *06 September 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-17* is/are pending in the application.

4a) Of the above claim(s) *1,6-10,13,14,16 and 17* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *2-5,11,12 and 15* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *1.5* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

1. Applicant's election with traverse of Group II, claims 2-4, 11, 12, and 5 and 15 in part in Paper No. 9 is acknowledged. The traversal is on the ground(s) that regardless of the Examiner's citation of Motoyama...there would not be an undue burden of search and/or consideration for the Examiner to examine claims 1-17" and the response then addresses PCT Rule 13 as far as certain combinations of different categories of claims are permissible such as product, manufacture of said product and use of product. (see pages 3-4 of response). This is not found persuasive because PCT Rule 13.1 states that to have a general inventive concept the inventions need to be linked by a special technical feature. As evidenced by Motoyama et al the technical feature in claim 1 is not special and as such the groups are not so linked as to form a single general concept under PCT Rule 13.1. Therefore the restriction is proper and in addition, the response did not rebut the Motoyama reference. As to the question of burden of search, the literature search, particularly relevant in this art, is not co-extensive and is much more important in evaluating the burden of search. Clearly different searches and issues are involved in the examination of each group. For these reasons the restriction requirement is deemed to be proper and is made **FINAL**.

2. Claims 1, 6-10, 13-14, 16-17 and 5 and 15 in part are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected inventions. Applicant timely traversed the restriction (election) requirement in Paper No. 9. Claims 5 and 15 are withdrawn to the extent the claims read on a polypeptide.

3. Claims 2-4, 11, 12, and 5 and 15 in part are under examination. Claims 5 and 15 will be examined to the extent they read on a nucleic acid.

Claim Objections

4. Claims 2-4, 5, 11-12, and 15 are objected to because of the following informalities:

a. The claims depend from non-elected claim 1. For examination purposes the limitations of claim 1 will be included in claims depending on claim 1 .

b. Claim 4 contains a typographical error in the term "hybridising".

c. Claims 5 and 15 contain subject matter that was not elected, i.e. the polypeptide.

Appropriate correction is required.

Claim Rejections - 35 USC § 112

5. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

6. Claims 2-4, 5, 1-12, and 15 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

a. Claims 2-4, 5, 11-12, and 15 are indefinite for reciting "capable of participating in the human PTCH/SHH pathway" in claim 1 because the phrase is not clear. Does the protein participate in the pathway or not and what does "participating" encompass? Does participating mean directly binds the SHH or does the protein interact with another protein that has some involvement with the SHH protein or PTCH proteins?

b. Claim 4 is indefinite for reciting "capable of specifically hybridising" because the exact meaning of the phrase is not clear. It is unclear what full set of conditions are contemplated for the hybridization.

c. Claim 5 is indefinite for reciting "use as a medicament" because the phrase is not clear. Does the phrase mean for use in a method or as a composition or some other meaning?

7. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

8. Claim 15 is rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claim 15 recites a kit for the detection of human PTCH2 gene. The claim encompasses any PTCH2 gene, however, the specification only teaches the gene for

PTCH2 as SEQ ID NO:5 which encodes SEQ ID NO:1. The specification does not disclose what structural and functional characteristics are needed to function as a PTCH2 gene, therefore one skilled in the art would not know what a PTCH2 gene was or what the proteins structure is. The claims encompass a genus of nucleic acids, however, the specification only teaches one species of SEQ ID NO:5. Therefore, it is reasonable to conclude that the claim encompasses subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

9. Claim2-4, 5, 11-12, and 15 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a nucleic acid that encodes SEQ ID NO:1 and a nucleic acid that encodes Ptch2 and patched-2 and vectors, host cells, and kits comprising such nucleic acids and compositions comprising such, does not reasonably provide enablement for any nucleic acid that encodes an analogue or variant of SEQ ID NO:1 or any nucleic acid that hybridizes to the nucleic acid that encodes SEQ ID NO:1 or any variant or analogue thereof or any vectors or host cells comprising such or kits comprising such for the detection of any PTCH2 gene or compositions comprising such . The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

Factors to be considered in determining whether undue experimentation is required, are summarized in Ex parte Forman, 230 USPQ 546 (BPAI 1986). They include the nature of the invention, the state of the prior art, the relative skill of those in the art, the amount of direction or guidance disclosed in the specification, the presence or absence of working examples, the predictability or unpredictability of the art, the breadth of the claims, and the quantity of experimentation which would be required in order to practice the invention as claimed.

The claims are broadly drawn to any nucleic acid that encodes a analogue, variant which is essentially SEQ ID NO:1 and nucleic acids which hybridize to such and variants of such nucleic acids and vectors and host cells comprising such and compositions comprising such and kits comprising a variant nucleic acid for detection of any PTCH2 gene. The specification teaches the DNA encoding SEQ ID NO:1 and the gene encoding SEQ ID NO:1, SEQ ID NO:5, and vectors and host cells comprising such. The specification also teaches that PTCH2 mRNA was observed exclusively in the tumor cells of al BCCs (see page 23, line 7). The specification teaches spliced variants but does not enable a function for the variants.

The claims are not commensurate in scope with the enablement provided in the specification. The claims encompass nucleic acids that encode analogs and variants that would not function as SEQ ID NO:1, as well as nucleic acids for the detection of any PTCH2 gene wherein it is not clear what structural and functional characteristics are encompassed by a PTCH2 gene that encodes a PTCH2 protein.

Protein chemistry is probably one of the most unpredictable areas of biotechnology. For example, the replacement of a single lysine at position 118 of the acidic fibroblast growth factor by a glutamic acid led to a substantial loss of heparin binding, receptor binding, and biological activity of the protein (see Burgess et al, Journal of Cell Biology Vol 111 November 1990 2129-2138). In transforming growth factor alpha, replacement of aspartic acid at position 47 with asparagine, did not affect biological activity while the replacement with serine or glutamic acid sharply reduced the biological activity of the mitogen (see Lazar et al Molecular and Cellular Biology Mar 1988 Vol 8 No 3 1247-1252).

Replacement of the histidine at position 10 of the B-chain of human insulin with aspartic acid converts the molecule into a superagonist with 5 times the activity of nature human insulin. Schwartz et al, Proc Natl Acad Sci USA Vol 84:6408-6411 (1987). Removal of the amino terminal histidine of glucagon substantially decreases the ability of the molecule to bind to its receptor and activate adenylate cyclase. Lin et al Biochemistry USA Vol 14:1559-1563 (1975).

These references demonstrate that even a single amino acid substitution or what appears to be an inconsequential chemical modification, will often dramatically affect the biological activity of the protein.

Although biotechnology has made great strides in the recent past, these references serve to demonstrate exactly how little we really know about the art. Elucidation of the genetic code induces one to believe that one can readily obtain a

functional synthetic protein for any known nucleic acid sequence with predictable results.

Claim 4 recites an isolated nucleic acid that hybridizes to any nucleic acid that encodes a analogue or variant of SEQ ID NO:1. The claim encompasses nucleic acids that would not encode a protein that functions as SEQ ID NO:1 and the claim does not recite the specific conditions for hybridization. The specification discloses "stringent conditions" as conditions which a probe will hybridize to its target sequence, but no other sequence (see page 9, lines 7-11) and the specification discloses stringent conditions are sequence dependent and will be different in different circumstances. While the specification does disclose stringent conditions, it is not clear what full set of conditions are contemplated in the claim and as evidenced from the specification the conditions will be different in different circumstances. Thus, one skill in the art would not know which conditions are set forth in claim 4.

In view of the lack of predictability in the art of protein chemistry as evidenced by Lazar, Burgess, Lin, and Schwartz and in view of the myriad of nucleic acids that are encompassed by the claims that would not encode a functioning protein and in view of the lack of guidance in the specification, lack of examples, and lack of predictability associated with regard to producing and using the myriad of derivatives encompassed in the scope of the claims, one skilled in the art would be forced into undue experimentation in order to practice the broadly claimed invention.

Claim Rejections - 35 USC § 102

10. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in-
> (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effect under this subsection of a national application published under section 122(b) only if the international application designating the United States was published under Article 21(2)(a) of such treaty in the English language; or
> (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that a patent shall not be deemed filed in the United States for the purposes of this subsection based on the filing of an international application filed under the treaty defined in section 351(a).

11. Claims 2-4, 5, 11-12 are rejected under 35 U.S.C. 102(b) as being anticipated by Motoyama et al (Nature Genetics 18:104-106, 2/98, IDS #11/2).

The claims recite a nucleic acid that encodes an analog or variant capable of participating in the human PTCH/SHH pathway during embryonic development and/or carcinogenesis which is essentially comprised of SEQ ID NO:1, a vector comprising such, and a host cell comprising a vector. For this rejection the intended use recited in claim 5 of the nucleic acid for a medicament is being interpreted to be a composition comprising the nucleic acid.

Motoyama et al teach the nucleic acid encoding Ptch2 which is highly homologous (97% see attached sequence alignment on the back of this Office action) to the protein of SEQ ID NO:1 which is a variant of SEQ ID NO:1, and the cDNA was cloned (see Figure 1). It is inherent that the cloning of the nucleic acid was in a vector and the vector was in a host cell. In addition, since the protein of Motoyama et al is a

variant PTCH protein it would be inherent that the protein could participate in the human pathway in an in vitro setting because of the high homology of SEQ ID NO:1 and the protein of Motoyama et al.

12. Claims 2-4, 5, 11-12 rejected under 35 U.S.C. 102(e) as being anticipated by Sauvage et al (U.S. Patent 6,348,575, with priority to 4/15/98).

The claims and the interpretation of claim 5 has been described supra.

Sauvage et al teach a nucleic acid that encodes Patched-2 of humans and the protein is highly homologous to SEQ ID NO:1 (99.7%, see the attached sequence alignment on the back of this Office Action) and vectors and host cell comprising such (see column 13-17). In addition, since the protein of Sauvage et al is a PTCH protein it would be inherent that the protein would participate in the human PTCH pathway in carcinogenesis because of the high homology of SEQ ID NO:1 and the protein of Sauvage et al.

13. Claim 4 is rejected under 35 U.S.C. 102(b) as being anticipated by the Boehinger Mannheim 1991 catalog.

The claim has been described supra.

The Boehinger Mannheim catalog teaches random primers that would hybridize to a nucleic acid that encoded SEQ ID NO:1.

Claim Rejections - 35 USC § 103

14. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

15. Claims 2-4, 5, 11-12, and 15 are rejected under 35 U.S.C. 103(a) as being unpatentable over Motoyama et al (Nature Genetics 18:104-106, 2/98, IDS 1 ½).

Claims 2-4, 5, 11-12 have been described supra. Claim 15 recites a kit for detection of human PTCH2 gene comprising in a container a nucleic acid molecule. For this rejection the intended use of the kit for detection is given no patentable weight.

Motoyama et al has been described supra. Motoyama et al does not exemplify a kit comprising in a container a nucleic acid.

Although claim 15 recites a kit, no positive recitation of the kit ingredients/elements distinguishes the claim over the references. Therefore, the references read on the claimed kit. Further, it is a well-known convention in the art to place the recited elements in a kit comprising a container for the advantages of convenience and economy.

Thus, the claimed subject matter is considered obvious over the prior art, absent sufficient factual evidence to the contrary.

16. Claims 2-4, 5, 11-12, and 15 are rejected under 35 U.S.C. 103(a) as being unpatentable over Sauvage et al (U.S. Patent 6,348,575, with priority to 4/15/98).

The claims have been described supra. For this rejection the intended use of the kit for detection is given no patentable weight.

Sauvage et al has been described supra. Sauvage et al does not exemplify a kit comprising in a container a nucleic acid.

Although claim 15 recites a kit, no positive recitation of the kit ingredients/elements distinguishes the claim over the references. Therefore, the references read on the claimed kit. Further, it is a well-known convention in the art to

place the recited elements in a kit comprising a container for the advantages of convenience and economy.

Thus, the claimed subject matter is considered obvious over the prior art, absent sufficient factual evidence to the contrary.

Conclusion

17. No claim is allowed. The prior art made of record and not relied upon is considered pertinent to applicant's disclosure. U.S. Patent 6,309,879.

18. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Larry R. Helms, Ph.D, whose telephone number is (703) 306-5879. The examiner can normally be reached on Monday through Friday from 7:00 am to 4:30 pm, with alternate Fridays off. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony Caputa, can be reached on (703) 308-3995. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

19. Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the

Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center telephone number is (703) 308-4242.

Respectfully,

Larry R. Helms Ph.D.

703-306-5879